Peer Review File

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Review Comments

Reviewer A

The authors reported a case of a giant middle mediastinal leiomyosarcoma.
The paper deals with an important issue and is well written. I have some comments as follows:

Abstract
P2, line 29-30: If primary mediastinal leiomyosarcoma is accounting for approximately 15% of all primary mediastinal sarcomas, isn't "extremely rare" a bit of an overstatement?

Reply: *Rare cancers are defined by EURACAN as a cancer affecting less than 6 per 100 000 individuals a year (=60 per million per year) (https://euracan.eu/rare-adult-solid-cancers/introduction-on-rare-cancers/, reached on December 10, 2021). The maximal incidence of soft tissue sarcoma is 200 per million per year (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma/incidence#heading-One, reached on December 12, 2021). Primary mediastinal sarcomas represent ~1% of all soft tissue sarcomas (Burt M, Ihde JK, Hajdu SI, et al. Primary sarcomas of the mediastinum: results of therapy. J Thorac Cardiovasc Surg 1998;115:671–80.). Therefore, the incidence of primary mediastinal sarcoma is around 2 per million per year. Primary mediastinal leiomyosarcoma accounts for less than 15% of all primary mediastinal sarcoma. As a consequence, incidence of primary mediastinal leiomyosarcoma is about 0.3 individuals per million per year, which is 200 times less common than the definition of a rare cancer.*

The term "extremely rare" is therefore in our opinion not overstated. This point of view was also shared by Moran et al in his abstract (Moran CA et al: Malignant smooth muscle neoplasms presenting as mediastinal soft tissue masses. Clinicopathologic study of 10 cases. Cancer, Vol.74: 2251-2260, 1994). The manuscript was not modified.

Introduction

P3, line 56-57: The authors described as follows: Most mediastinal tumors arise from the anterior mediastinal compartment. Is this true? Isn't that an overstatement?

Reply: *No, it is true according to Reference 2. Reference 2 was added to this statement in the manuscript for more clarity (P 3, L 56).*

Case Report

P4, line 71, 76, 85, and 86: Please spell "COPD", "CT", "PET/CT", and "MRT" in full.

Reply: *Acronyms were spelled in full. The manuscript was changed accordingly.*

P4, line 79-80: Why did the authors perform EBUS-TBNA instead of transesophageal EUS-FNA for tissue sampling in this case? The latter is more likely to yield more tissue, don't you think?

Reply: *Both were possible and would yield a cytological diagnosis. Your opinion is biased due to Figure 2. But as we could prove it, EBUS-FNA was possible, free of complication. No change was made to the manuscript.*

P5, line 94-95: What extent of lymph node dissection was performed?

Reply: *Paratracheal, subcarinal and hilar lymph node dissection was performed. We modified the manuscript as suggested (P5, L 92).*

Also, is there a defined extent of lymph node dissection that should be performed

in this case? Is it necessary to perform a lymph node dissection in the first place?

Reply: *Due to the rarity of the disease, there is no consensus recommendation on the extend of lymph node dissection. We decided to perform lymph node dissection due to its very low morbidity. No change was made to the manuscript.*

P5, line 98-99: What does "Tumor margins were free of tumor." mean? Does it mean that the authors combined resected the surrounding tissue? Does it mean that the tumor was covered by a membrane? Please describe it in detail.

Reply: *All around the tumor, there was a plane that made the complete resection of the tumor possible, without resection of any surrounding structure as it is already described in the text (P 5, L 91). To avoid confusion, the term "sharply dissected" was added to the manuscript on P 4, L 90.*

Discussion

P6-7, line 135-139: Where was pathogenesis presumed to have originated in this case pathologically? Please provide additional discussion.

Reply: *Additional hypothesis as well as a reference were added in the manuscript (P 7, L137-140).*

P7, line 149-150: What is the general treatment strategy for cases like this one? Please state clearly. Was there any consideration given to preoperative treatment in this case?

Reply: *Due to the rarity of these cases, there is no consensus recommendation available yet. I hope that the EURACAN Thoracic Sarcoma Initiative will be able to suggest treatment algorithm in a near future. A preoperative treatment with Doxorubicin-based chemotherapy was discussed, but due to patient age and symptom burden, an upfront surgical treatment was chosen as already mentioned in the manuscript (P4, L85-86). No change was made to the manuscript.*

Reviewer B

Nice report of an extremely rare tumor; this case is worth publishing - just a few comments below with a small suggested revision/inclusion to clarify the tumor was not attached to any vessels.

Major comment:

Line 127: were molecular studies conducted in this particular case as mentioned in line 27? Or does this statement refer to molecular testing in general; this should be clarified.

One important reason is that the main differential for leiomyosarcoma of the mediastinum is intimal sarcoma; the primary histology of which is leiomyosarcoma histology. Intimal sarcomas are usually associated with great vessels (as are leiomyosarcomas - likely an biproduct of multiple reported cases being mis-classified/diagnosed) and are characterized by MDM2 amplification in 50% or more of cases.

The report mentions that this tumor was not associated with any structures; but does not specifically mention that it was distant from the great vessels - I would add this specific fact and possibly mention the differential of intimal sarcoma was excluded clinically/surgically as the tumor arose separately from any obvious vessels. This would be important to mention particularly if MDM2 molecular testing was not performed.

Reply: *Thank you for your relevant remark. MDM2 molecular testing was not performed since intimal sarcoma was intraoperatively excluded. The manuscript was modified accordingly (P5, L 96-98).*

Minor comment:

Line 80: change to "Spindle cell complexes were noted on microscopy"

Reply: *Change was made.*

Line 81: Change IHC stains to "CD34" and "CD56" (no spaces).

Reply: *Change was made.*

Reviewer C

The authors present a case of a mediastinal leiomyosarcoma that originated from the soft tissues of the mediastinum rather than from one of ten adjacent organs. The review of the literature done by the authors is incomplete. They failed to mention the series by Moran et al (Moran CA et al: Malignant smooth muscle neoplasms presenting as mediastinal soft tissue masses. Clinicopathologic study of 10 cases. Cancer, Vol.74: 2251-2260, 1994) in which a similar phenomenon is described.

Reply: *Thank you for your remark. We discussed the paper and added the reference in the manuscript (P 6 and 7 , L133-135 and 137-139).*